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30. (Amended) A method as defined in claim 21, wherein said proteasome inhibitor is [lactocystein] lactacystin or an analog thereof.

31. (Amended) A method as defined in claim 24, wherein said proteasome inhibitor is [lactocystein] lactacystin or an analog thereof.

#### REMARKS

Applicants have read and considered the Office Action dated July 12, 2000. Claims 21 and 24-31 remain in the case. Claims 21, 24, 30 and 31 have been amended to further distinguish over the prior art, while claims 18-20 have been cancelled without prejudice or disclaimer as being directed to a non-elected subject matter. Reconsideration and re-examination are hereby requested.

Claim 21 has been amended to define a method wherein the concentration of proteasome inhibitors is defined in the reference to the concentrations of lactacystin that have been specifically detailed. A key feature of this invention is to have demonstrated that a proteasome inhibitor (whichever it is) is capable of reversing an ongoing undesirable reaction selectively in activated cells.

Claims 22 and 23 have been cancelled. These modifications are believed to overcome the Examiner's rejection under 35 U.S.C. 112, first paragraph.

Claims 30 and 31 have been rejected under the 35 U.S.C. 112, first paragraph. These claims have been amended to define lactacystin, which is the specific compound that has been detailed in the specification.

Claims 21-31 have been rejected under 35 U.S.C. 112, second paragraph, as failing to point out the subject matter Applicant regards as his invention. The ongoing "action" that is referred to in the claims has been properly defined as proliferation or activity or both. The terms "administering an effective amount of proteasome" have been changed to "contacting said cells with an [effective] amount". The amount would be equivalent to about 6 to 20  $\mu\text{M}$  of lactacystin as a reference compound. Numerous proteasome inhibitors are known, namely from Schreiber et al. There is no reason why this invention should be limited to lactacystin.

Claim 25 has been rejected as being indefinite because the claim recites cyclosporin A, rapamycin and FK506, and Applicant has elected one specie: rapamycin. The election of one specie was made to respond to the preceding Office Action wherein it was required "under 35 U.S.C. 121 to elect a disclosed specie for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable". It was Applicant's understanding that any immunosuppressive drug, which includes the three drugs mentioned in claim 25, would be covered, if a generic claim is allowable.

Claim 27 depends on claim 21 and not on claim 26. Therefore, Applicant does not see any contradiction or ambiguity in the fact that claim 26 defines cell death, while claim 27 defines energy and oxygen deprivation.

The spelling of term "lactacystin" has been corrected in claims 30 and 31.

The Examiner has rejected claims 21-24, 30 and 31 under 35 U.S.C. 102(b) as being anticipated by Schreiber et al. (WO 96/32105). Applicant does not share this view. Schreiber et al. do not provide any support to the fact that a proteasome inhibitor could reverse an ongoing adverse reaction. Thus, although Schreiber et al. disclose a "treatment which includes [...] reversing, reducing or arresting the symptoms, clinical signs and underlying pathology of a condition in a manner to improve or stabilize the subject's condition", they do not provide any supporting evidence, not even in vitro results, to the effect that lactacystin is capable of reversing an ongoing action of blood cells. Conversely, the present inventor has provided ample support, in vitro, to such a reversal of an ongoing proliferation and activity of activated blood cells. The inventor provides guidance to the skilled reader as to how and when to administer the inhibitor (when = after activation, which provides selectivity to the treatment towards activated cells versus resting cells), this guidance being totally absent from the applied reference. It is therefore respectfully requested that this ground of rejection be removed.

Claims 21-31 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Schreiber et al. in view of Armistead et al. (US 5,665,774) and Imajoh-Ohmi et al. It is respectfully submitted that none of the secondary references cures the deficiency of teachings by Schreiber et al. that a proteasome inhibitor is capable of reversing an ongoing action of activated blood cells. Imajoh-Ohmi et al. disclose that lactacystin has a response that is similar in monoblast U937 cells whether interferon gamma is added or not. This means that the cells respond to lactacystin, whenever they are activated or not by the cytokine. The results shown in

Figure 1 indicate that lactacystin does not respond like the reference apoptotic compound TNF $\alpha$ , the latter being more active in activated cells than in non-activated cells. Imajoh-Ohmi et al. therefore do not teach or suggest a method wherein blood cells are activated first and then submitted to lactacystin to reverse an ongoing proliferation. This reference does not teach any selectivity of lactacystin vis-à-vis activated cells, compared to a lack of effect towards resting cells. Without trying to explain the discrepancy between the teachings of Imajoh-Ohmi and the present disclosure, it is clear that this reference teaches away from the present invention.

It is respectfully submitted that the claims as amended are allowable over the art of record or any combination thereof.

A speedy and favorable action is earnestly solicited. If the Examiner believes a telephone interview would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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